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**WEST****End of Result Set**☐ **Generate Collection**

L15: Entry 11 of 11

File: USPT

Mar 15, 1994

US-PAT-NO: 5294441DOCUMENT-IDENTIFIER: US 5294441 A

TITLE: Avirulent microbes and uses therefor: salmonella typhi

DATE-ISSUED: March 15, 1994

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/200.1; 424/235.1, 424/258.1, 435/252.3, 435/252.33, 435/320.1,  
435/879

## CLAIMS:

## We claim:

1. An immunogenic composition for the immunization of an individual comprising a live avirulent *S. typhi* obtained from a pathogenic *S. typhi* strain, said avirulent *S. typhi* made avirulent by of an inactivating mutation in the structural *cya* gene and an inactivating mutation in the structural *crp* gene.
2. An immunogenic composition according to claim 1, wherein said avirulent *S. typhi* is a recombinant gene from an agent pathogenic to said individual, to produce an antigen which induces an immune response in said individual against said pathogen.
3. A method for stimulating the immune system of an individual to respond to an immunogenic antigen of *S. typhi* comprising administering to said individual the immunogenic composition comprising a live avirulent *S. typhi* obtained from a pathogenic *S. typhi* strain, said avirulent *S. typhi* made avirulent by an inactivating mutation in the structural *cya* gene and an inactivating mutation in the structural *crp* gene.
4. A method for stimulating the immune system of an individual to respond to an immunogenic antigen of a pathogen comprising administering to said individual an immunogenic composition comprising a live avirulent *S. typhi* obtained from a pathogenic *S. typhi* strain, said avirulent *S. typhi* made avirulent by an inactivating mutation in the structural *cya* gene and an inactivating mutation in the structural *crp* gene wherein said avirulent *S. typhi* expresses a recombinant gene from an agent pathogenic to said individual, to produce an antigen which induces an immune response in said individual against said pathogen.
5. An isolated avirulent strain of *S. typhi* obtained from a pathogenic strain of *S. typhi* said avirulent *S. typhi* made avirulent by an inactivating mutation in the structural *cya* gene and an inactivating mutation in the structural *crp* gene.
6. The isolated avirulent strain of *S. typhi* of claim 5 which expresses a recombinant gene from an agent pathogenic to an individual, to produce an antigen which induces an immune response in said individual against said pathogen.
7. A strain according to claim 6 wherein the *S. typhi* contains a chromosomal mutation which is lethal and which is balanced by a vector borne gene which complements the lethal mutation to constitute a balanced-lethal host-vector system.
8. A strain according to claim 7 wherein cells of the strain;
  - (a) lack a functioning native chromosomal gene encoding .beta.-aspartate semialdehyde dehydrogenase (*asd*);
  - (b) have present an exogenously introduced gene encoding a functional *Asd* polypeptide which phenotypically complements the chromosomal *asd* mutation, but which cannot replace

the defective chromosomal gene by recombination; and

(c) have a physical linkage between the genes encoding the functional Asd polypeptide and the immunogenic antigen, wherein the loss of the gene encoding the functional Asd polypeptide causes the cells to lyse when the cells are in an environment in which the lack of functional Asd causes the cells to lyse.

9. A strain according to claim 5 that has the characteristics of .chi.3927.

10. An immunogenic composition according to claim 1 comprised of a strain according to claim 9.

11. A method of preparing an immunogenic composition by suspending in a physiological excipient, an avirulent *S. typhi* obtained from a pathogenic strain of *S. typhi*, the avirulent *S. typhi* having an inactivating mutation in the structural *cya* gene and an inactivating mutation in the structural *crp* gene.

12. A method according to claim 4 wherein said live avirulent *S. typhi* also

(a) lacks a functioning native chromosomal gene encoding .beta.-aspartate semialdehyde dehydrogenase (*asd*);

(b) has present an exogenously introduced gene encoding a functional Asd polypeptide which phenotypically complements the chromosomal *asd* mutation, but which cannot replace the defective chromosomal gene by recombination; and

(c) has physical linkage between the genes encoding the functional Asd polypeptide and the immunogenic antigen, wherein the loss of the gene encoding the functional Asd polypeptide causes the cells to lyse when the cells are in an environment in which the lack of functional Asd causes the cells to lyse.

**WEST****End of Result Set**

Generate Collection

L13: Entry 9 of 9

File: USPT

Feb 7, 1995

US-PAT-NO: 5387744

DOCUMENT-IDENTIFIER: US 5387744 A

TITLE: Avirulent microbes and uses therefor: Salmonella typhi

DATE-ISSUED: February 7, 1995

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A
Kelly; Sandra M.	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/258.1; 435/252.3, 435/252.33, 435/320.1, 435/879

## CLAIMS:

We claim:

1. An immunogenic composition for the immunization of an individual comprising a live avirulent Salmonella having a mutation in a cdt gene said live avirulent Salmonella having the phenotype of failure to colonize deep tissue of Salmonella deposit strain ATCC no. 55113.
2. An immunogenic composition for the immunization of an individual according to claim 1, wherein said avirulent Salmonella expresses a recombinant gene from an agent pathogenic to said individual, to produce an antigen which induces an immune response in said vertebrate against said pathogen.
3. A method for stimulating the immune system of an individual to respond to an immunogenic antigen of Salmonella comprising administering to said individual an immunogenic composition comprising a live avirulent Salmonella having a mutation in a cdt gene said live avirulent Salmonella having the phenotype of failure to colonize deep tissue of Salmonella deposit strain ATCC no. 55113.
4. A method for stimulating the immune system to respond to an immunogenic antigen of a pathogen comprising administering to said individual an immunogenic composition comprising a live avirulent Salmonella having a mutation in a cdt gene said live avirulent Salmonella having the phenotype of failure to colonize deep tissue of Salmonella deposit strain ATCC no. 55113.
5. A biologically pure live avirulent strain of Salmonella said live avirulent Salmonella having the phenotype of failure to colonize deep tissue of Salmonella deposit strain ATCC no. 55113.
6. The avirulent strain of Salmonella of claim 5, which expresses a recombinant gene from an agent pathogenic to said individual, to produce an antigen which induces an immune response in said vertebrate against said pathogen.
7. A strain according to claim 6, wherein the Salmonella contains a chromosomal mutation which is lethal and which is balanced by a vector-borne gene which complements the lethal mutation to constitute a balanced lethal host vector system.
8. A strain according to claim 6, wherein cells of the strain:
  - a) lack a functioning native chromosomal gene encoding beta-aspartate semialdehyde dehydrogenase asd;
  - b) have present an exogenously introduced gene encoding a functional Asd polypeptide which phenotypically complements the chromosomal asd mutation, but which cannot replace the defective chromosomal gene by recombination; and
  - c) have a physical linkage between the recombinant genes encoding the functional Asd

polypeptide and the immunogenic antigen, wherein the loss of the recombinant gene encoding the functional Asd polypeptide causes the cells to lyse when the cells are in an environment in which the lack of functional Asd causes the cells to lyse.

9. A live biologically pure strain of *S. typhi* having a mutation in a *cdt* gene said live avirulent *Salmonella* having the phenotype of failure to colonize deep tissue of *Salmonella* deposit strain ATCC no. 55113.

10. A vaccine for the immunization of an individual comprising:  
a pharmaceutically effective mount of a live avirulent *Salmonella* which has a diminished ability to colonize deep tissue of said individual as a result of a mutation in a *cdt* gene said live avirulent *Salmonella* having the phenotype of failure to colonize deep tissue of *Salmonella* deposit strain ATCC no. 55113.

11. The vaccine of claim 10 wherein said avirulent *Salmonella* fails to colonize deep tissue of said individual. 2

**WEST****End of Result Set**☐ **Generate Collection**

L12: Entry 6 of 6

File: USPT

Feb 14, 1995

US-PAT-NO: 5389368DOCUMENT-IDENTIFIER: US 5389368 A

TITLE: Avirulent microbes and uses therefor

DATE-ISSUED: February 14, 1995

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gurtiss, III; Roy	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/200.1; 424/93.4, 435/252.3, 435/252.33, 435/320.1

## CLAIMS:

What is claimed is:

1. A vaccine for the immunization of a vertebrate or invertebrate comprising a live avirulent bacterium selected from the group consisting of Salmonella, Escherichia and Salmonella-Escherichia hybrids obtained from a pathogenic strain of said bacterium, said pathogenic strain of said bacterium containing a gene encoding adenylate cyclase and a gene encoding cyclic AMP receptor protein and said strain of said bacterium made avirulent by an inactivating mutation in the gene encoding adenylate cyclase and an inactivating mutation in said gene encoding cyclic AMP receptor protein, and wherein upon administration with a pharmaceutically acceptable carrier to said vertebrate or invertebrate, said live avirulent bacteria is effective in evoking an immune response in said vertebrate or invertebrate to immunize against said pathogenic strain.
2. The vaccine according to claim 1 wherein said bacterium is Salmonella typhimurium.
3. A vaccine for the immunization of a vertebrate or invertebrate comprising a live avirulent bacterium selected from the group consisting of Salmonella, Escherichia, and Salmonella-Escherichia hybrids obtained from a pathogenic strain of said bacterium that contains a gene encoding adenylate cyclase and a gene encoding cyclic AMP receptor protein, said pathogenic strain of said bacterium made avirulent by an inactivating mutation in the gene encoding adenylate cyclase and in the gene encoding cyclic AMP receptor protein, and wherein said strain of said bacterium also expresses a heterologous gene from a pathogenic microorganism to said vertebrate or invertebrate to produce an antigen wherein upon administration with a pharmaceutically acceptable carrier said vaccine effects an immune response in said vertebrate or invertebrate against said pathogenic microorganism.
4. The vaccine according to claim 3 wherein said bacterium is Salmonella typhimurium.
5. The vaccine according to claim 3 wherein said pathogenic microorganism is selected from the group consisting of viruses, bacteria, protozoa, parasites and fungi.
6. The vaccine according to claim 5 wherein said pathogenic microorganism is a bacterium selected from the group consisting of Neisseria gonorrhoeae, Chlamydia trachomatis, Streptococcus mutans, Mycobacterium tuberculosis, Mycobacterium leprae, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema palladium, Neisseria meningitidis, Mycoplasma pneumoniae, Hemophilus influenzae, Bordetella pertussis, Bordetella avium, Escherichia coli, and Streptococcus equi.
7. A method for stimulating the immune system in a vertebrate or invertebrate, comprising the step of:  
administering to said vertebrate or invertebrate an amount of a live avirulent bacterium selected from the group consisting of Salmonella, Escherichia, and

Salmonella-Escherichia hybrids obtained from a pathogenic strain of said bacterium, said pathogenic strain of said bacterium containing a gene encoding adenylate cyclase and a gene encoding cyclic AMP receptor protein and said strain of said bacterium made avirulent by an inactivating mutation in the gene encoding adenylate cyclase and an inactivating mutation in said gene encoding cyclic AMP receptor protein which effective in evoking an immune response in said vertebrate or invertebrate to immunize against said pathogenic strain.

8. (Twice amended) The method according to claim 7 wherein said bacterium is Salmonella typhimurium.

9. The method according to claim 7 wherein said administering is accomplished by the introduction of the vaccine by means of oral ingestion, gastric intubation, aerosols, intravenous, intramuscular, subcutaneous, intramammary, intrapenial or intravaginal injection.

10. A live avirulent Salmonella, Escherichia, or Salmonella-Escherichia hybrid which contains a gene encoding adenylate cyclase and a gene encoding cyclic AMP receptor protein, said Salmonella, Escherichia, or Salmonella-Escherichia hybrid made avirulent by an inactivating mutation in a gene encoding adenylate cyclase and an inactivating mutation in a gene encoding cyclic AMP receptor protein.

11. The vaccine according to claim 2 wherein said bacterium is a strain selected from the group .chi.4062 (ATCC 53647), and .chi.4064 (ATCC 53648; or a strain retaining the vaccine properties of ATCC 53647 and ATCC 53648.



**WEST**

Generate Collection

L11: Entry 8 of 9

File: USPT

Oct 7, 1997

US-PAT-NO: 5674736

DOCUMENT-IDENTIFIER: US 5674736 A

TITLE: Salmonella virulence genes

DATE-ISSUED: October 7, 1997

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miller, III; Samuel I.	Brookline	MA	N/A	N/A
Mekalanos; John J.	Cambridge	MA	N/A	N/A

US-CL-CURRENT: 435/252.3; 424/258.1, 424/93.2, 435/245, 435/252.8

## CLAIMS:

What is claimed is:

1. A Salmonella cell the virulence of which is attenuated by a deletion in the phoQ gene.
2. The Salmonella cell of claim 1, further comprising a virulence attenuating mutation in a phoP regulatory region gene.
3. The Salmonella cell of claim 2, wherein said virulence attenuating mutation is in the phoP gene.
4. The Salmonella cell of claim 2, wherein said virulence attenuating mutation is in a prg locus.
5. The Salmonella cell of claim 4, wherein said virulence attenuating mutation is in the prgH gene.
6. The Salmonella cell claim 4, wherein said virulence attenuating mutation is in the prgA, prgB, prgC, or prgE gene.
7. The Salmonella cell of claim 2, wherein said virulence attenuating mutation is in a pag locus.
8. The Salmonella cell of claim 7, wherein said virulence attenuating mutation is a pagC mutation.
9. The Salmonella cell of claim 1, wherein said cell is of the species S. typhi.
10. The Salmonella cell of claim 1, wherein said cell is of the species S. enteritidis and of the strain typhimurium.
11. The Salmonella cell of claim 1, wherein said Salmonella cell is of the species S. cholerae-suis.

**WEST****End of Result Set**

Generate Collection

L11: Entry 9 of 9

File: USPT

Jun 13, 1995

US-PAT-NO: 5424065DOCUMENT-IDENTIFIER: US 5424065 A

TITLE: Vaccines containing avirulent phop-type microorganisms

DATE-ISSUED: June 13, 1995

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A
Galan; Jorge	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/93.2; 424/184.1, 424/93.48, 435/252.3, 435/252.8, 435/69.1, 435/71.1

## CLAIMS:

We claim:

1. A vaccine for immunizing an individual against disease symptoms caused by Salmonella, said vaccine being comprised of avirulent Salmonella which contain a mutation in the phoP gone, wherein said avirulent Salmonella are unable to cause Salmonella-based disease symptoms and able to colonize in lymphoid tissue for a sufficient time to induce antibody and cellular immunity, and wherein said avirulent Salmonella retain the properties of avirulence and immunogenicity of a Salmonella strain selected from the group consisting of ATCC number 53864, ATCC number 53865, and ATCC number 53866.
2. The vaccine of claim 1, wherein the avirulent Salmonella are admixed with a pharmaceutically acceptable excipient.
3. A vaccine for immunizing an individual against disease caused by a pathogenic microorganism, wherein said vaccine is comprised of carrier Salmonella cells which contain a mutation in the phoP gene which renders said carrier Salmonella cells avirulent and immunogenic, wherein said carrier Salmonella cells are transformed with a recombinant expression vector encoding an immunogenic antigen from said pathogenic microorganism, and wherein said carrier Salmonella are unable to cause Salmonella-based disease symptoms and able to colonize in lymphoid tissue for a sufficient time to induce antibody and cellular immunity, and wherein said carrier Salmonella retain the properties of avirulence and immunogenicity of a Salmonella strain selected from the group consisting of ATCC number 53864, ATCC number 53865, and ATCC number 53866.
4. The vaccine of claim 3, wherein the carrier Salmonella cells are admixed with a pharmaceutically acceptable excipient.
5. A method of immunizing an individual against a disease caused by Salmonella comprising administering to said individual the vaccine of claim 1, at an immunologically effective dose.
6. A method of immunizing an individual against a disease caused by Salmonella comprising administering to said individual the vaccine of claim 2, at an immunologically effective dose.
7. A method of immunizing an individual for disease symptoms caused by a pathogenic microorganism, comprising administering to said individual the vaccine of claim 3 at an immunologically effective dose.
8. A method of immunizing an individual for disease symptoms caused by a pathogenic microorganism, comprising administering to said individual the vaccine of claim 4 at an immunologically effective dose.

9. A method of making a vaccine which comprises admixing (1) an immunologically effective dose of avirulent Salmonella which contain a mutation in the phoP gene wherein said avirulent Salmonella are unable to cause Salmonella-based disease symptoms and able to colonize in lymphoid tissue for a sufficient time to induce antibody and cellular immunity, and wherein said avirulent Salmonella retain the properties of avirulence and immunogenicity of a Salmonella strain selected from the group consisting of ATCC number 53864, ATCC number 53865, and ATCC number 53866 with (2) a pharmaceutically acceptable carrier.

10. A method of making a vaccine which comprises admixing (1) an immunologically effective dose of carrier Salmonella cells which are avirulent and immunogenic wherein said carrier Salmonella cells contain a mutation in the phoP gene, wherein said carrier Salmonella cells are transformed with a recombinant expression vector encoding an immunogenic antigen from a pathogenic microorganism, and wherein said carrier Salmonella are unable to cause Salmonella-based disease symptoms and able to colonize in lymphoid tissue for a sufficient time to induce antibody and cellular immunity, and wherein said carrier Salmonella retain the properties of avirulence and immunogenicity of a Salmonella strain selected from the group consisting of ATCC number 53864, ATCC number 53865, and ATCC number 53866 with (2) a pharmaceutically acceptable carrier.

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Generate Collection

L11: Entry 7 of 9

File: USPT

Dec 9, 1997

US-PAT-NO: 5695983

DOCUMENT-IDENTIFIER: US 5695983 A

TITLE: Salmonella vaccines

DATE-ISSUED: December 9, 1997

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miller; Samuel I.	Brookline	MA	N/A	N/A
Mekalanos; John J.	Cambridge	MA	N/A	N/A

US-CL-CURRENT: 435/252.8; 435/245

## CLAIMS:

What is claimed is:

1. A Salmonella cell, the virulence of which is attenuated by a mutation in one or more genes selected from the group consisting of pagJ, pagK, pagM, and msgA.
2. The Salmonella cell of claim 1, wherein said mutation is in pagJ.
3. The Salmonella cell of claim 1, wherein said mutation is in pagK.
4. The Salmonella cell of claim 1, wherein said mutation is in pagM.
5. The Salmonella cell of claim 1, wherein said mutation is in msgA.

**WEST**

Generate Collection

L11: Entry 5 of 9

File: USPT

Dec 1, 1998

US-PAT-NO: 5843426

DOCUMENT-IDENTIFIER: US 5843426 A

TITLE: Salmonella vaccines

DATE-ISSUED: December 1, 1998

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miller; Samuel I.	Seattle	WA	N/A	N/A
Mekalanos; John J.	Cambridge	MA	N/A	N/A

US-CL-CURRENT: 424/93.2; 424/235.1, 435/252.3

## CLAIMS:

We claim:

1. A vaccine comprising a Salmonella typhi Ty800 cell, said cell comprising a mutation in the phoQ gene, wherein said mutation attenuates virulence and does not result in the insertion of an antibiotic resistance gene into said phoQ gene.

**WEST****End of Result Set**☐ **Generate Collection**

L10: Entry 5 of 5

File: USPT

Nov 21, 1995

US-PAT-NO: 5468485DOCUMENT-IDENTIFIER: US 5468485 A

TITLE: Avirulent microbes and uses therefor

DATE-ISSUED: November 21, 1995

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/184.1; 424/200.1, 424/93.1, 424/93.2, 435/252.3, 435/252.33,  
435/252.8, 435/69.1, 435/71.1

## CLAIMS:

I claim:

1. A vaccine for immunization of an individual comprising a live avirulent *S. choleraesuis* obtained from a pathogenic strain of *S. choleraesuis*, said avirulent *S. choleraesuis* being made avirulent by an inactivating mutation in a *cya* gene and an inactivating mutation in a *crp* gene.
2. A vaccine for the immunization of an individual according to claim 1, wherein said avirulent *S. choleraesuis* expresses in the individual a recombinant gene derived from an agent which is pathogenic to said individual, to produce an antigen which induces an immune response in said individual against said pathogen.
3. A vaccine according to claim 2, wherein said individual is a vertebrate.
4. A method for stimulating the immune system to respond to an immunogenic antigen of *S. choleraesuis* comprising administering to an individual a live avirulent *S. choleraesuis* obtained from a pathogenic strain of *S. choleraesuis*, said avirulent *S. choleraesuis* being made avirulent by an inactivating mutation in a *cya* gene and an inactivating mutation in a *crp* gene.
5. A method for stimulating the immune system to respond to an immunogenic antigen of a pathogen comprising administering to an individual a live avirulent *S. choleraesuis* obtained from a pathogenic strain of *S. choleraesuis*, said avirulent *S. choleraesuis* being made avirulent by an inactivating mutation in a *cya* gene and an inactivating mutation in a *crp* gene and which expresses in said individual a recombinant gene encoding the immunogenic antigen, to produce an antigen capable of inducing an immune response in said individual against said pathogen.
6. A method according to claim 5, wherein said individual is a vertebrate.

**WEST****End of Result Set**

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L9: Entry 2 of 2

File: USPT

Aug 12, 1997

US-PAT-NO: 5656488DOCUMENT-IDENTIFIER: US 5656488 A

TITLE: Recombinant avirulent salmonella antifertility vaccines

DATE-ISSUED: August 12, 1997

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A
Tung; Kenneth S. K.	Charlottesville	VA	N/A	N/A

US-CL-CURRENT: 435/252.33; 424/184.1, 424/200.1, 435/252.3, 435/252.8, 435/69.3,  
530/395

## CLAIMS:

We claim:

1. An avirulent microbe derived from a pathogenic gram negative microorganism selected from the group consisting of Salmonella, Escherichia, and Salmonella-Escherichia hybrids comprising a recombinant expression system which encodes at least one gamete-specific antigen that is displayed on the surface of gametes exposed during the process leading to fertilization, wherein the avirulent microbe, upon administration to an individual, is capable of colonizing a lymphoreticular tissue and eliciting a mucosal immune response.
2. An avirulent microbe according to claim 1, wherein the avirulent microbe lacks a functioning native chromosomal gene encoding beta-aspartate semialdehyde dehydrogenase (Asd), and further wherein the microbe comprises a recombinant gene encoding a functional Asd polypeptide, the recombinant gene being linked to one or more genes encoding one or more gamete-specific antigens.
3. An avirulent microbe according to claim 1, wherein the avirulent microbe comprises a mutated cya gene such that the microbe is substantially incapable of producing functional adenylate cyclase.
4. An avirulent microbe according to claim 1, wherein the avirulent microbe comprises a mutated crp gene such that the microbe is substantially incapable of producing functional cyclic AMP receptor protein.
5. An avirulent microbe according to claim 2, wherein the avirulent microbe further comprises a mutated cya gene and a mutated crp gene such that the microbe is substantially incapable of producing functional adenylate cyclase and functional cyclic AMP receptor protein.
6. An avirulent microbe according to claim 1, wherein the microbe is *S. typhimurium*.
7. An avirulent microbe according to claim 1, wherein the microbe is an *E. coli*-Salmonella hybrid.
8. An avirulent microbe according to claim 1, wherein the gamete-specific antigen is lactic dehydrogenase-C.
9. An avirulent microbe according to claim 1, wherein the gamete-specific antigen is SP-10.
10. An avirulent microbe according to claim 1 wherein the gamete-specific antigen is ZP-3.
11. An avirulent microbe according to claim 5, wherein the gamete-specific antigen is lactic dehydrogenase-C.

12. An avirulent microbe according to claim 5, wherein the gamete-specific antigen is SP-10.
13. An avirulent microbe according to claim 5 wherein the gamete-specific antigen is ZP-3.
14. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 1, in combination with a pharmaceutically acceptable vehicle.
15. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 5, in combination with a pharmaceutically acceptable vehicle.
16. A method for inducing an antifertility state in a vertebrate subject, said method comprising administering to said subject an effective amount of a vaccine composition according to claim 14.
17. A method for inducing an antifertility state in a vertebrate subject, said method comprising administering to said subject, an effective amount of a vaccine composition according to claim 15.
18. A method according to claim 16, wherein the gamete-specific antigen is lactic dehydrogenase-C.
19. A method according to claim 16, wherein the gamete-specific antigen is SP-10.
20. A method according to claim 16, wherein the gamete-specific antigen is ZP-3.
21. A method according to claim 17, wherein the gamete-specific antigen is lactic dehydrogenase-C.
22. A method according to claim 17, wherein the gamete-specific antigen is SP-10.
23. A method according to claim 17, wherein the gamete-specific antigen is ZP-3.
24. An avirulent microbe according to claim 1 wherein the gamete-specific antigen is a sperm-specific antigen.
25. An avirulent microbe according to claim 24 wherein the sperm-specific antigen is selected from the group consisting of lactate dehydrogenase-C and SP-10.
26. An avirulent microbe according to claim 1 wherein the gamete-specific antigen is an ovum-specific antigen.
27. An avirulent microbe according to claim 5 wherein the gamete-specific antigen is a sperm-specific antigen.
28. An avirulent microbe according to claim 5 wherein the sperm-specific antigen is selected from the group consisting of lactate dehydrogenase-C and SP-10.
29. An avirulent microbe according to claim 5 wherein the gamete-specific antigen is an ovum-specific antigen.
30. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 24, in combination with a pharmaceutically acceptable vehicle.
31. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 25, in combination with a pharmaceutically acceptable vehicle.
32. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 26, in combination with a pharmaceutically acceptable vehicle.
33. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 27, in combination with a pharmaceutically acceptable vehicle.
34. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 28, in combination with a pharmaceutically acceptable vehicle.
35. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 29, in combination with a pharmaceutically acceptable vehicle.
36. A method according to claim 16, wherein the gamete-specific antigen is a sperm-specific antigen.
37. A method according to claim 36, wherein the sperm-specific antigen is selected from the group consisting of lactate dehydrogenase-C and SP-10.
38. A method according to claim 16 wherein the gamete-specific antigen is an ovum-specific antigen.
39. A method according to claim 17, wherein the gamete-specific antigen is a sperm-specific antigen.
40. A method according to claim 17, wherein the sperm-specific antigen is selected from the group consisting of lactate dehydrogenase-C and SP-10.
41. A method according to claim 17 wherein the gamete-specific antigen is an



ovum-specific antigen.

42. The avirulent microbe according to claim 1 wherein said avirulent microbe is capable of eliciting a mucosal immune response to lactic dehydrogenase-C.

43. The avirulent microbe according to claim 1 wherein said avirulent microbe is capable of eliciting a mucosal immune response to SP-10.

44. The avirulent microbe according to claim 1 wherein said avirulent microbe is capable of eliciting a mucosal immune response to ZP-3.

45. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 42.

46. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 43.

47. A vaccine composition comprising a therapeutically effective amount of an avirulent microbe according to claim 44.

48. A method for inducing an antifertility state in a vertebrate subject, said method comprising administering to said subject an effective amount of a vaccine composition according to claim 45.

49. A method for inducing an antifertility state in a vertebrate subject, said method comprising administering to said subject an effective amount of a vaccine composition according to claim 46.

50. A method for inducing an antifertility state in a vertebrate subject, said method comprising administering to said subject an effective amount of a vaccine composition according to claim 42.

**WEST****End of Result Set**☐ **Generate Collection**

L6: Entry 2 of 2

File: USPT

Jan 5, 1999

US-PAT-NO: 5855879DOCUMENT-IDENTIFIER: US 5855879 A

TITLE: Avirulent microbes and uses therefor

DATE-ISSUED: January 5, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss III; Roy	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/93.2; 424/184.1, 424/200.1, 424/235.1, 424/257.1, 424/258.1,  
424/93.48, 435/252.3, 435/252.33, 435/320.1, 435/879

## CLAIMS:

We claim:

1. An immunogenic composition for the immunization of an individual comprising a derivative of a pathogenic gram negative bacteria made avirulent by an inactivating mutation in a crp gene, in a pharmaceutically acceptable carrier.
2. An immunogenic composition for the immunization of an individual according to claim 1 wherein the avirulent derivative of a pathogenic gram negative bacteria is capable of expressing a recombinant gene derived from an agent which is pathogenic to said individual, to produce an antigen capable of inducing an immune response in said vertebrate against said pathogenic agent.
3. A method for stimulating the immune system to respond to an immunogenic antigen of a pathogenic gram negative bacteria comprising administering to said individual the immunogenic composition of claim 1.
4. A method for stimulating the immune system to respond to an immunogenic antigen of a pathogen comprising administering to said individual the immunogenic composition of claim 2.
5. An isolated gram negative bacterial strain comprising a derivative of a pathogenic gram negative bacteria made avirulent by an inactivating mutation in a crp gene wherein said derivative is capable of invading and persisting in the gut-associated lymphoid tissue or bronchus-associated lymphoid tissue.
6. The isolated bacterial strain of claim 5 which is capable of expressing a recombinant gene derived from an agent which is pathogenic to an individual, to produce an antigen capable of inducing an immune response in said individual against said pathogenic agent.
7. A strain according to claim 6, wherein the avirulent strain of a pathogenic gram negative bacteria contains a chromosomal mutation which is lethal, balanced by a vector gene which complements the lethal mutation to constitute a balanced-lethal host-vector system.
8. A strain according to claim 7, wherein cells of the strain:
  - a) lack a functioning native chromosomal gene encoding beta-aspartate semialdehyde dehydrogenase (Asd);
  - b) have present a recombinant gene encoding a functional Asd polypeptide which complements the chromosomal asd mutation, but which cannot replace the defective chromosomal gene by recombination;
  - c) have a physical linkage between the recombinant genes encoding the functional Asd polypeptide and the immunogenic antigen, wherein the loss of the recombinant gene

encoding the functional Asd polypeptide causes the cells to lyse when the cells are in an environment in which the lack of functional Asd causes the cells to lyse.

9. A method of utilizing a strain of a pathogenic gram negative bacteria made avirulent by a mutation in a crp gene, the method comprising preparing an immunogenic composition by combining the strain with a pharmaceutically acceptable carrier.

**WEST****End of Result Set**☐ **Generate Collection**

L3: Entry 1 of 1

File: USPT

Mar 30, 1999

US-PAT-NO: 5888799

DOCUMENT-IDENTIFIER: US 5888799 A

TITLE: Recombinant avirulent bacterial antigen delivery system

DATE-ISSUED: March 30, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 435/252.3; 424/184.1, 424/257.1, 424/258.1, 435/243, 435/252.8

## CLAIMS:

What is claimed as new and desired to be secured by Letters Patent of the United States is:

1. An antigenic preparation comprising an avirulent derivative of a pathogenic bacterial species which expresses a product of a nucleic acid sequence coding for an antigen of a pathogenic organism or infectious disease agent of a vertebrate host, wherein said product of said nucleic acid sequence coding for said antigen of said pathogenic organism or infectious disease agent does not possess a cross reacting antigenic determinant with said vertebrate host and wherein said avirulent derivative and said pathogenic organism or infectious disease agent do not normally exchange genetic information, thereby requiring use of recombinant DNA cloning to achieve expression of said product of said nucleic acid sequence in said avirulent derivative and wherein said antigenic preparation homes to lymphoid tissue or a lymphoepithelial structure of said vertebrate host and induces an immune response in said vertebrate host upon administration thereto.
2. A method of inducing an immune response in a vertebrate host which comprises administering to said vertebrate host an antigenic preparation comprising an avirulent derivative of a pathogenic bacterial species which expresses a product of a nucleic acid coding for an antigen of a pathogenic organism or infectious disease agent of a vertebrate host, wherein said product of said nucleic acid sequence coding for said antigen of said pathogenic organism or infectious disease agent does not possess a cross reacting antigenic determinant with said vertebrate host and wherein said avirulent derivative and said pathogenic organism or infectious disease agent do not normally exchange genetic information, thereby requiring use of recombinant DNA cloning to achieve expression of said product of said nucleic acid sequence in said avirulent derivative and wherein said antigenic preparation homes to lymphoid tissue or a lymphoepithelial structure of said vertebrate host and induces an immune response in said vertebrate host upon administration thereto.
3. A method of making an antigenic preparation which comprises transforming an avirulent derivative of a pathogenic bacterial species with a nucleic acid sequence coding for an antigen of a pathogenic organism or infectious disease agent of a vertebrate host wherein said product of said nucleic acid sequence coding for said antigen of said pathogenic organism or infectious disease agent does not possess a cross reacting antigenic determinant with said vertebrate host and wherein said avirulent derivative and said pathogenic organism or infectious disease agent do not normally exchange genetic information thereby requiring use of recombinant DNA cloning to achieve expression of said product of said nucleic acid sequence in said avirulent

derivative and wherein said antigenic preparation homes to lymphoid tissue or a lymphoepithelial structure of said vertebrate host and induces an immune response in said vertebrate host upon administration thereto.

4. A recombinant avirulent derivative of a pathogenic bacterial species which expresses a product of a nucleic acid sequence coding for an antigen of a pathogenic organism or infectious disease agent of a vertebrate host, wherein said product of said nucleic acid sequence coding for said antigen of said pathogenic organism or infectious disease agent does not possess a Cross reacting antigenic determinate with said vertebrate host and wherein said avirulent derivative and said pathogenic organism or infectious disease agent do not normally exchange genetic information, thereby requiring use of recombinant DNA cloning to achieve expression of said product of said nucleic acid sequence in said avirulent derivative and wherein said recombinant avirulent derivative of a pathogenic bacterial species homes to lymphoid tissue or a lymphoepithelial structure of said vertebrate host and induces an immune response in said vertebrate host upon administration thereto.

5. An antigenic preparation according to claim 1 wherein said avirulent derivative of a pathogenic bacterial species is selected from the group consisting of Salmonella, E. coli, and Salmonella-E. coli hybrids.

6. A method of inducing an immune response in a vertebrate host according to claim 2 wherein said avirulent derivative of a pathogenic bacterial species is selected from the group consisting of Salmonella, E. coli, and Salmonella-E. coli hybrids.

7. A method of making an antigenic preparation according to claim 3 wherein said avirulent derivative of a pathogenic bacterial species is selected from the group consisting of Salmonella, E. coli, and Salmonella-E. coli hybrids.

8. A recombinant avirulent derivative of a pathogenic bacterial species according to claim 4 wherein said pathogenic bacterial species is selected from the group consisting of Salmonella, E. coli, and Salmonella-E. coli hybrids.

**WEST****End of Result Set**☐ **Generate Collection**

L8: Entry 7 of 7

File: USPT

Sep 30, 1997

US-PAT-NO: 5672345DOCUMENT-IDENTIFIER: US 5672345 A

TITLE: Selective maintenance of a recombinant gene in a population of vaccine cells

DATE-ISSUED: September 30, 1997

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/93.2; 435/252.3, 435/69.1, 435/71.2

## CLAIMS:

I claim:

1. A live bacterial carrier for a vaccine for immunizing an individual, said carrier comprising an avirulent derivative of a pathogenic strain of bacteria characterized by:

- a) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd);
- b) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
- c) the presence of a second recombinant gene encoding a desired polypeptide; and
- d) physical linkage between the first recombinant gene and the second recombinant gene, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival.

2. The live bacterial carrier according to claim 1 wherein said bacterial carrier is formulated in a pharmaceutically acceptable excipient in a pharmacologically effective dose.

3. The live bacterial carrier of claim 1, wherein the avirulent derivative of a pathogenic strain of bacteria is a Salmonella.

4. The live bacterial carrier of claim 3, wherein the first recombinant gene encodes Asd derived from Streptococcus mutans.

5. The live bacterial carrier of claim 4, wherein the second recombinant gene encodes an antigenic determinant encoded with the spaA gene of S. mutans.

6. The live bacterial carrier of claim 5, wherein the first recombinant gene encodes Asd derived from S. typhimurium.

7. A composition for stimulating an immune response in an individual comprising a live avirulent derivative of a pathogenic strain of bacteria characterized by:

- a) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd);
- b) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
- c) the presence of a second recombinant gene encoding a desired polypeptide; and
- d) physical linkage between the first recombinant gene and the second recombinant gene, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival.

8. The composition of claim 7, wherein the avirulent derivative of a pathogenic strain

of bacteria is a Salmonella.

9. The composition of claim 8, wherein the first recombinant gene encodes Asd derived from *S. mutans*.
10. The composition of claim 9, wherein the second recombinant gene encodes an antigenic determinant encoded within a *spaA* gene of *S. mutans*.
11. The composition of claim 10, wherein the first recombinant gene encodes Asd derived from *S. typhimurium*.
12. A method of immunizing an individual comprising administering the live bacterial carrier for a vaccine of claim 1 to the individual.
13. A method of stimulating the immune system of an individual comprising administering the composition of claim 7 to the individual.
14. A method of preparing a bacterial carrier for a vaccine for immunization of an individual, said method comprising:
  - a) providing an avirulent derivative of a pathogenic strain of bacteria characterized by:
    - 1) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd)
    - 2) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
    - 3) the presence of a second recombinant gene encoding a desired polypeptide; and
    - 4) physical linkage between the first recombinant gene and the second recombinant gene, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival;
  - b) providing a suitable excipient; and
  - c) mixing the bacteria with the excipient in a suitable pharmacologic dose.
15. An immunogenic composition comprising an avirulent derivative of a pathogenic strain of bacteria characterized by:
  - a) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd);
  - b) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
  - c) the presence of a second recombinant gene encoding a desired polypeptide; and
  - d) physical linkage between the first recombinant gene and the second recombinant gene, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival.
16. The composition of claim 15 wherein the second recombinant gene encodes an antigenic determinant encoded within a *spaA* gene of *S. mutans*.

**WEST****End of Result Set**

Generate Collection

L5: Entry 3 of 3

File: USPT

Jan 5, 1999

US-PAT-NO: 5855880

DOCUMENT-IDENTIFIER: US 5855880 A

TITLE: Avirulent microbes and uses therefor

DATE-ISSUED: January 5, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Curtiss, III; Roy	St. Louis	MO	N/A	N/A
Kelly; Sandra M.	St. Louis	MO	N/A	N/A

US-CL-CURRENT: 424/93.2; 424/184.1, 424/200.1, 424/235.1, 424/257.1, 424/258.1,  
424/93.48, 435/252.3, 435/252.33, 435/320.1, 435/879

## CLAIMS:

We claim:

1. An immunogenic composition for the immunization of an individual comprising a derivative of a pathogenic gram negative bacteria made avirulent by an inactivating mutation in a cya gene, in a pharmaceutically acceptable carrier.
2. An immunogenic composition for the immunization of an individual according to claim 1, wherein the avirulent derivative of a pathogenic gram negative bacteria is capable of expressing a recombinant gene derived from an agent which is pathogenic to said individual, to produce an antigen capable of inducing an immune response in said vertebrate against said pathogenic agent.
3. A method for stimulating the immune system to respond to an immunogenic antigen of a pathogenic gram negative bacteria comprising administering to said individual the immunogenic composition of claim 1.
4. A method for stimulating the immune system to respond to an immunogenic antigen of a pathogen comprising administering to said individual the immunogenic composition of claim 2.
5. An isolated gram negative bacterial strain comprising a derivative of a pathogenic gram negative bacteria made avirulent by an inactivating mutation in a cya gene wherein said derivative is capable of invading and persisting in the gut-associated lymphoid tissue or bronchus-associated lymphoid tissue.
6. The isolated bacterial strain of claim 5 which is capable of expressing a recombinant gene derived from an agent which is pathogenic to an individual, to produce an antigen capable of inducing an immune response in said individual against said pathogenic agent.
7. A strain according to claim 6, wherein the avirulent strain of the pathogenic microbe contains a chromosomal mutation which is lethal, balanced by a vector which complements the lethal mutation to constitute a balanced lethal host-vector system.
8. A strain according to claim 7, wherein cells of the strain:
  - a) lack a functioning native chromosomal gene encoding beta-aspartate semialdehyde dehydrogenase (Asd);
  - b) have present a recombinant gene encoding a functional Asd polypeptide which complements the chromosomal asd mutation, but which cannot replace the defective chromosomal gene by recombination;
  - c) have a physical linkage between the recombinant genes encoding the functional Asd polypeptide and the immunogenic antigen, wherein the loss of the recombinant gene



encoding the functional Asd polypeptide causes the cells to lyse when the cells are in an environment in which the lack of functional Asd causes the cells to lyse.

9. A method of utilizing a strain of a pathogenic gram negative bacteria made avirulent by a mutation in a cya gene, the method comprising preparing an immunogenic composition by combining the strain with a pharmaceutically acceptable carrier.